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An algorithm for quantitatively estimating non-occupational pesticide exposure intensity for spouses in the Agricultural Health Study

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Abstract

Residents of agricultural areas experience pesticide exposures from sources other than direct agricultural work. We developed a quantitative, active ingredient specific algorithm for cumulative

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(adult, married lifetime) non occupational pesticide exposure intensity for spouses of farmers who applied pesticides in the Agricultural Health Study (AHS). The algorithm addressed three exposure pathways: take home, agricultural drift, and residential pesticide use. Pathway-specific equations combined (i) weights derived from previous meta analyses of published pesticide exposure data and (ii) information from the questionnaire on frequency and duration of pesticide use by applicators, home proximity to treated fields, residential pesticide usage (e.g., termite treatments), and spouse's off farm employment (proxy for time at home). The residential use equation also incorporated a published probability matrix that documented the likelihood active ingredients were used in home pest treatment products. We illustrate use of these equations by calculating exposure intensities for the insecticide chlorpyrifos and herbicide atrazine for 19,959 spouses. Non zero estimates for ≥1 pathway were found for 78% and 77% of spouses for chlorpyrifos and atrazine, respectively. Variability in exposed spouses' intensity estimates was observed for both pesticides, with 75th to 25th percentile ratios ranging from 7.1−7.3 for take home, 6.5−8.5 for drift, 2.4−2.8 for residential use, and 3.8−7.0 for the summed pathways. Take home and drift estimates were highly correlated (≥0.98), but were not correlated with residential use (0.01−0.02). This algorithm represents an important advancement in quantifying non occupational pesticide relative exposure differences and will facilitate improved etiologic analyses in the AHS spouses. The algorithm could be adapted to studies with similar information.

INTRODUCTION

Pesticide exposure for people living in agricultural areas can occur via multiple pathways. These pathways may include occupational exposure from personal use of pesticides on farms, take-home exposure from the transfer of pesticides from skin, clothes, and shoes of agricultural workers to the family home, agricultural drift exposure from living near fields or orchards where pesticides are applied, and residential use exposure from pesticide treatments of insects and weeds in and around the home (Deziel et al. 2015b). Most epidemiologic studies of cancer risk from agricultural pesticide exposure have focused on a single pathway, i.e., the occupational pathway, which likely provides the largest contribution to total exposure. However, non-occupational pathways may be important contributors to pesticide exposure for residents in agricultural areas and need to be characterized to maximize power to detect associations. This may be particularly important for family members of occupational pesticide users, who may not experience direct occupational pesticide exposures, or may experience these exposures at a lower frequency, duration, or magnitude.

In epidemiologic studies, non-occupational pesticide exposure in agricultural areas has typically been characterized using surrogate exposure metrics from participant-reported information. These metrics usually account for only one exposure pathway and have limited information on specific chemicals or on the frequency and duration of exposure (Blair and Zahm 1990; Hoppin et al. 2006). Surrogates used to characterize non-occupational exposures include duration of living on a farm (Carreon et al. 2005; Folsom et al. 1996), proximity to treated fields (Aschengrau et al. 1996), treatment of residential pests (Glorennec et al. 2017), or laundering pesticide laden clothing (Carreon et al. 2005; Duell et al. 2000). Other studies have used geographic information system-based methods that incorporated crop maps or satellite imagery to calculate the density of crops near a residence to predict possible pesticide exposures (Glorennec et al. 2017; Cockburn et al. 2011; Ward et al. 2006; Rull and Ritz 2003), although such data may only be intermittently available or may lack the spatial resolution needed to identify individual crop characteristics (Maxwell et al. 2010). Some studies have also used biomarkers of exposure, which are aggregate measures of pesticide exposure from all pathways (Alexander et al. 2006; Alexander et al. 2007; Arbuckle and Ritter 2005; Curwin et al. 2007). Due to the short half lives of many pesticide biomarkers, they rarely represent the long-term exposure relevant for cancer or other chronic disease evaluations (Barr et al. 2006).

An alternative approach is to use a transparent decision rule based framework that links subject-reported information to quantitative measures, which has been used in several studies to estimate historical occupational exposures (Dopart and Friesen 2017; Negatu et al. 2016). For example, an occupational pesticide exposure algorithm, previously developed for the prospective cohortof >52,000 licensed pesticide applicators in the Agricultural Health Study (AHS), combines subject reported information on the frequency of mixing pesticides, application methods, and personal protective equipment usage with weighting factors derived from the literature, expert judgment, and field evaluation studies (Coble et al. 2011; Dosemeci et al. 2002; Hines et al. 2008). The occupational algorithm-based intensity estimates have demonstrated good correlation with exposure monitoring data (Coble et al. 2005; Thomas et al. 2010). These intensity estimates have been combined with frequency and duration of pesticide use to obtain cumulative exposure estimates for epidemiologic analyses.

Here, we used a decision rule-based approach to develop a deterministic algorithm that quantitatively estimates cumulative (i.e., over adult married life) exposure intensity for a specific active ingredient from three non-occupational pesticide exposure pathways for spouses of the AHS pesticide applicators. The ‘AHS spouses’ comprise 32,345 spouses (99% female) of pesticide applicators who sought private, restricted-use pesticide licenses in Iowa and North Carolina in 1993–97. These spouses reported diverse levels of participation in farming activities, with approximately 50% not engaged in any pesticide application related activities at enrollment (Gladen et al. 1998; Louis et al. 2017). They provide a unique population in which to study the impact of pesticide exposure on chronic disease risks, including female-specific outcomes, at pesticide exposure levels anticipated to be at the high end of the non-occupationally exposed population (Alavanja et al. 1994; Kirrane et al. 2004). In addition, this group will allow follow-up on suggestive findings in the female AHS applicators (n=1,563) within a much larger population of exposed; for example, the observation of a suggested increased risk of ovarian cancer among female applicators exposed to atrazine (Freeman et al. 2011).

The non-occupational spouse pesticide algorithm described here provides quantitative estimates of cumulative pesticide exposure intensity for the take-home, agricultural drift, and residential pesticide use pathways for single pesticide active ingredients. These pathways were selected based on evidence from the literature that higher pesticide concentrations in house dust were associated with farm work done by one or more home residents (take-home), shorter distances between homes and treated fields (drift), and greater home use of pesticides to treat pests in and around the home (residential use) (Deziel et al. 2015b). Other exposure pathways, though plausible, were not consistently supported by the literature (e.g., dietary ingestion). The non-occupational spouse algorithm described here uses a similar approach to the above-mentioned applicator occupational pesticide algorithm (Dosemeci et al. 2002; Coble et al. 2011); however, it directly incorporates frequency and duration of pesticide applications into pathway-specific equations to estimate cumulative exposure and represents multiple pathways rather than a single pathway. In this paper, we present the derivation of the non-occupational algorithm. To illustrate its application, we calculated pathway-specific intensity estimates separately for the insecticide chlorpyrifos and herbicide atrazine in a subset of AHS spouses. Chlorpyrifos and atrazine were selected because they were commonly measured in the published pesticide house dust studies and were frequently used in the AHS cohort (Deziel et al. 2015b; Deziel et al. 2017).

METHODS: ALGORITHM DEVELOPMENT AND EXAMPLE CALCULATIONS

Algorithm Overview

To estimate spouse-specific, cumulative (adult, married life) non-occupational exposure intensity for a single active ingredient (*ai*) ($E_{non\text{-}occ,ai}$), we developed active ingredient (*ai*) specific equations for each of the take home ($E_{take\text{-}home,ai}$), agricultural drift ($E_{drift,ai}$), and residential pesticide use ($E_{res,ai}$) pathways in units of intensity-weighted years. The overall framework is shown in Figure 1 and each pathway is described in detail below. These pathway equations can be used singly or combined depending on the plausibility of their contributions for a given active ingredient. For example, the residential use pathway can be dropped for those active ingredients never licensed for residential use. If all pathways are deemed relevant and assumed to have equal weight, the pathway-specific estimates may be summed to obtain an overall cumulative pesticide exposure intensity across the three pathways [Eq. 1].

$$E_{non-occ,ai} = E_{take-home,ai} + E_{drift,ai} + E_{res,ai} \quad [1]$$

Each of the equations were based on our findings from a qualitative literature review that identified factors predicting relative differences in pesticide exposure among households and individuals in agricultural areas (Deziel et al. 2015b). We used pesticide concentrations in house dust as surrogates for non-occupational exposures, because house dust measurements integrate pesticide levels over months or years (Deziel et al. 2013; Lewis et al. 1994) and exhibited sufficient variability and detection rates among agricultural households in published studies. We abstracted published dust concentrations across a range of pesticide active ingredients and used meta-regression models to quantify the average relative contributions of the pathways to pesticide concentrations in house dust (Deziel et al. 2017) to provide the pathway weights. We used individual-level information from responses to AHS questionnaires administered to the spouses and applicators to identify exposure differences among the AHS spouses. The questionnaires provided active ingredient-specific information, including duration and frequency of agricultural use of each active ingredient by the applicator, as well as information on household characteristics (e.g., distance between the home and nearest treated fields; home pest treatment practices), and the spouse's off-farm employment as a surrogate for estimating time spent at home (http://aghealth.nih.gov/collaboration/questionnaires.html).

For illustrative purposes, we present descriptive statistics in the Results section for the calculated pathway-specific exposure intensities for chlorpyrifos and atrazine focusing on pesticide-use data collected at enrollment (1993–1997). We also required information related to cohabitation between spouses and partners, which was collected later in the study (2005–2010). We present these results for the subset of AHS spouses with complete information on cohabitation (n=19,064 for chlorpyrifos, n=19,077 for atrazine), which represents 60% of the total spouse cohort. Current efforts to reconstruct the cohabitation data for all spouses will facilitate future application of the algorithm to the full spouse cohort.

Duration Metrics

Duration metrics obtained from AHS questionnaires were used in all pathways to estimate cumulative exposure over adult, married life up to time of AHS enrollment. The take-home and agricultural drift pathways incorporated the applicator's number of days ($Days\ Applicator\ Applied_{ai}$) per year and years of active ingredient use while living with the spouse ($Years\ Applicator\ Applied\ While\ Together_{ai}$). We did not include the spouse's application days to avoid double-counting days when both spouse and applicator applied pesticides and to avoid overlap with the occupational pathway. Because the pathway-specific weights represent the average contribution aggregated over a long time span rather than the contribution per pesticide application day, we standardized $Days\ Applicator\ Applied_{ai}$ by dividing by the median number of days per year of any pesticide application reported across all applicators with at least one day of use at enrollment ($Median\ Application\ Days$=14.5), which reflected typical usage over the course of a substantial proportion of a farmer's working lifetime. $Years\ Applicator\ Applied\ While\ Together_{ai}$ was derived from the applicator's reported start and stop years of active ingredient use as well as the start and stop years of cohabitation, assuming continuous cohabitation. The residential pesticide use exposure pathway incorporated the number of years the spouse and applicator cohabitated ($Years\ Together$).

To illustrate the calculation of the algorithm, we present a hypothetical female spouse who lived with her husband for 18 years at enrollment ($Years\ Together$). Her husband applied both chlorpyrifos and atrazine for 15.5 of the 18 years in which they lived together ($Years\ Applicator\ Applied\ While\ Together_{chlorpyrifos} = Years\ Applicator\ Applied\ While\ Together_{atrazine}$ =15.5 yr). Her husband applied chlorpyrifos for "5–9 days in an average year" ($Days\ Applicator\ Applied_{chlorpyrifos}$ = 7 d/yr) and atrazine "10–19 days" ($Days\ Applicator\ Applied_{atrazine}$ =14.5 d/yr).

Take-Home Exposure Pathway

The take home exposure pathway captured pesticide exposure from the transfer of pesticides into the home from the skin, clothes, and shoes of applicators. Evidence that take-home exposure influenced pesticide concentrations in house dust came primarily from studies that identified higher concentrations of pesticides in house dust in homes of farmers who applied pesticides more frequently or recently compared to homes of farmers who did not apply pesticides or applied them less frequently or recently (Deziel et al. 2015b). Thus, for each active ingredient, we estimated the spouse's take-home exposure intensity ($E_{take\text{-}home,ai}$) as proportional to the spouse's average daily hours spent at the home divided by 24 (*Hours per Day Spouse at Home/24 hours*), the *Days Applicator Applied*$_{ai}$, and the *Years Applicator Applied While Together*$_{ai}$, with weight $k_{take\text{-}home}$ [Eq. 2]. We derived $k_{take\text{-}home}$ from our previous meta-analysis of house dust pesticide concentrations that found that homes of farmers with more frequent or recent pesticide application had 2.3 (95% CI: 1.5–3.3) times higher house dust pesticide concentrations than those of farmers with less frequent or recent pesticide use, based on 15 summary statistics reported in 5 studies (Deziel et al. 2017). Because the number of hours at home was not queried in the AHS questionnaires, *Hours per Day Spouse at Home* was based on the spouses' self-reported information about their longest-held job and employment-specific patterns of proportion of hours per day spent at home from the 2003 American Time Use Survey of women living in non-metropolitan areas (the earliest year of data available) (Bureau of Labor Statistics 2003). Spouses who had a year-round off-farm job ("full time"), spouses who had a part time job or who had a part-year full-time job ("part-time"), and spouses who worked neither part-time nor full-time outside the home ("no off-farm job") were assigned the survey's averages of 15.6, 17.8, and 21.0 hours/day at home, respectively. While we had data available on other behaviors typically used to characterize "take-home exposure", i.e., laundering pesticide-laden clothing or whether the applicator removed shoes/clothing prior to entering the house, we did not include these behaviors as modifiers at this time because our previously conducted literature review did not find strong support that these behavioral factors modified spouse's exposure to pesticides (Deziel et al. 2015b).

$$E_{take-home,ai} = k_{take-home} \times [Hours\ per\ Day\ Spouse\ at\ Home/24\ Hours\ per\ Day] \times \left[Days\ Applicator\ Applied_{ai}/Median\ Application\ Days\right] \times Years\ Applied\ While\ Together_{ai} \quad [2]$$

Therefore, if the hypothetical spouse described above never had an off-farm job (*Hours per Day Spouse at Home*=21 hours), her cumulative take-home exposure for chlorpyrifos would be 15 intensity-weighted years (calculation provided below); for atrazine it would be 31 intensity-weighted years (not shown).

$$E_{take-home,chlorpyrifos} = \left(2.3 \times \left[\frac{21}{24}\right] \times \left[\frac{7}{14.5}\right] \times 15.5\right) = 15\ \text{intensity} - \text{weighted years}$$

Agricultural Drift

The agricultural drift pathway captured pesticide exposure from the airborne transport of pesticides from the site of pesticide application to the home (rather than direct transfer from applicator). Evidence that agricultural drift influenced house dust pesticide concentrations came predominantly from studies that examined these concentrations at varying distances of the home to treated fields (Deziel et al. 2015b). Several studies also found that incorporating the quantity (mass) or density (mass per unit area) of active ingredients applied near the home yielded stronger associations with dust pesticide concentrations compared to proximity alone (Gunier et al. 2011; Harnly et al. 2009; Ward et al. 2006). In the AHS, however, spouses reported a categorical distance from the home to the nearest treated field (in English units), and we lacked information on amount applied, application rate, and formulation used with which to derive metrics of quantity or density of applied active ingredients. Additionally, the question about distance to treated fields was not linked to the applicator's pesticide use, so we assumed the applicator used the active ingredient at the fields nearest to the home and we were unable to account for drift occurring from pesticide usage on other nearby farms.

We estimated the spouse's exposure from agricultural drift ($E_{drift,\ ai}$) to be proportionally related to k_{drift}, the *Days Applicator Applied*$_{ai}$, and the *Years Applicator Applied While Together*$_{ai}$ [Eq. 3]. We derived k_{drift} from our previous meta regression analysis of the geometric mean (GM) dust pesticide concentrations at varying distances in ft (*d*) of the house from the fields for each distance response category (Table 1). For example, dust pesticide concentrations were predicted to be 3.0 times higher in homes <100 yd (<91 m) from treated fields, compared to homes >1/4 mile away (>402 m).

$$E_{drift,ai} = k_{drift} \times \left(Days\ Applicator\ Applied_{ai}/Median\ Application\ Days\right) \times Years\ Applied\ While\ Together_{ai} \quad [3]$$

For example, if our hypothetical spouse reported living "100–199 yards" (91 to 182 m) within treated fields, her k_{drift} value would be 1.9 (Table 1). Her cumulative agricultural drift estimate would be 14 intensity-weighted years for chlorpyrifos (calculation below) and 38 intensity-weighted years for atrazine.

$$E_{drift,chlorpyrifos} = \left(1.9 \times \left[\frac{7}{14.5}\right] \times 15.5\right) = 14\ intensity-weighted\ years$$

Residential Pesticide Use

The residential pesticide use pathway captured pesticide exposure that occurred from treating the home or pets for insects and the lawn, yard, or garden (hereafter, "lawn") for weeds. Evidence that residential pesticide use contributed to pesticide concentrations in house dust came primarily from findings of higher concentrations or detection rates in rural/agricultural households reporting treatment for specific home and lawn pests (e.g., weeds, fleas/ticks) compared to households that did not treat for those particular pests (Deziel et al. 2015a; Deziel et al. 2015b; Trunnelle et al. 2013). In these published studies, homeowners reported the type of pest treatment but did not provide specific active ingredients. Similarly, the AHS questionnaires queried spouses about whether household members or professionals performed several residential pest treatments (identified with subscript *trt*): termites, non-termite insects, flea/tick treatments applied in the home, flea/tick treatment directly to pets, and lawn weeds; these questions were not active ingredient-specific.

To obtain the likelihood of exposure to specific active ingredients for each treatment, we used a previously developed pesticide exposure probability matrix that synthesized market data on sales of commercial pest treatment products and active ingredients to estimate the probability that an active ingredient was used for different pest treatment scenario across various time frames (1976, 1980, 1990, 2000) (Colt et al. 2007; http://dceg.cancer.gov/tools/design/pesticide). Using this pesticide probability matrix, we mapped the spouses' questionnaire responses about the types of pest treatments and who applied them (household member, professional applicator, or other/don't know) to one or more of the matrix's pest treatment scenarios as described in Supplemental Table S1. Calculated probabilities by active ingredient are provided in Supplemental Table S2. We averaged the probabilities from 1976, 1980, and 1990 to derive the probabilities for treatments reported at enrollment.

We estimated that the residential use contribution to house dust concentrations for each pesticide active ingredient, $E_{res,ai}$, was proportional to whether the treatment occurred ($Treated_{trt}$) and the *Years Together*, with weight k_{res}. The value for k_{res} was either 1.3 (95% CI: 1.1–1.6) or 1.5 (95% CI: 1.2–1.9) if the probability of use for the pest treatment scenario from Supplemental Table S2 was ≥1% to <20% or ≥20%, respectively, based on our previous meta-regression analysis comparing treated versus untreated homes (88 statistics, 5 studies) (Deziel et al. 2017). *Years Together* was used because the frequency and duration of most of these treatments were not directly queried in the AHS questionnaire. The residential use contribution was summed across pest treatment types [Eq. 4].

$$E_{res,\,ai} = \left(k_{termites,\,ai} \times Treated_{termites} + k_{insects,\,ai} \times Treated_{insects} + k_{fleas\ home,\,ai} \times Treated_{fleas\ home} + k_{fleas\ pets,\,ai} \times Treated_{fleas\ pets} + k_{weeds,\,ai} \times Treated_{weeds}\right) \times Years\ Together \qquad [4]$$

For example, our hypothetical spouse reported that her home was treated for termites ($Treated_{termites}$=1), treated for non-termite insects by a professional ($Treated_{insects}$=1) and that her lawn was treated for weeds by a household member ($Treated_{weeds}$=1). She also reported that a flea/tick shampoo was used to treat a pet ($Treated_{fleas\ pets}$=1), but that her home was never treated for fleas/ticks by a fumigant/fogger bomb product ($Treated_{fleas\ home}$=0). The probability that chlorpyrifos was used in a termite treatment at enrollment was 0.24 (Supplemental Table S2), yielding a value of $k_{termites,chlorpyrifos}$ of 1.5. Similarly, based on probabilities of use, $k_{insects,chlorpyrifos}$, $k_{fleas\ home,chlorpyrifos}$, $k_{fleas\ pets,chlorpyrifos}$ = 1.3; these values were zero for atrazine because it is not an insecticide. For weed treatment by a household member, the pesticide exposure matrix yielded a probability of zero for both chlorpyrifos and atrazine ($k_{weeds,chlorpyrifos}$= $k_{weeds,atrazine}$=0).

Chlorpyrifos is an insecticide and therefore not used on weeds and atrazine is not commonly found in residential lawn products (Colt et al. 2007); its residential use is generally confined to Florida and the Southeast (USEPA 2003). Her cumulative residential pesticide use exposure estimate would be 74 and 0 intensity-weighted years for chlorpyrifos (calculation below) and atrazine, respectively.

$$E_{res,\, chlorpyrifos} = (1.5 \times 1 + 1.3 \times 1 + 1.3 \times 0 + 1.3 \times 1 + 0 \times 1) \times 18 = 74\ intensity - weighted\ years$$

RESULTS

Prevalence of Use and Duration Metrics

A substantial proportion of spouses experienced exposures through the take home and drift pathways due to the applicator's use, with 44% and 76% of applicators reporting usage of chlorpyrifos and atrazine, respectively (Table 2). The duration of use among those applying was shorter and spanned a narrower range for chlorpyrifos with a median of 3.5 yr (inter-quartile range [IQR]: 3.5–8.0) compared to 8.0 yr for atrazine (IQR: 3.5–25.5). Median application frequency among users was 7.0 d/y for both active ingredients, with a narrower IQR reported for chlorpyrifos (2.5–7.0) compared to atrazine (2.5–14.5).

Take-Home Exposure Pathway

Most spouses (73%) reported long-term, full time off farm jobs (and therefore were estimated to spend less time home), while 18% held part-time off-farm jobs, and 9% never held an off-farm job. The resulting median (IQR) cumulative exposure intensity estimates for the take-home pathway among those exposed was 2.5 (0.9–6.6) intensity weighted years for chlorpyrifos and 5.8 (2.1–15) intensity weighted years for atrazine, demonstrating a 7-fold ratio between the 75th and 25th percentiles for both active ingredients. The median intensity-weighted take-home estimate for exposed spouses was over two times higher for atrazine than for chlorpyrifos (5.8 vs. 2.5, respectively).

Agricultural Drift

The majority of spouses reported living within 200 yards of treated fields, with 47% of spouses assigned a distance between a home and treated field (d) of 150 ft (46 m), and 20% assigned 450 ft (137 m) (Table 2). Only 4% lived in the farthest category (1950 ft or 594 m). The median (IQR) cumulative exposure intensity estimates for the agricultural drift pathway among those exposed were 4.1 (1.7–11) for chlorpyrifos and 8.0 (2.6–22) for atrazine (Table 2), demonstrating ratios for the 75th to 25th percentiles of 6.5 and 8.5, respectively. The median intensity-weighted take-home estimate for exposed spouses was two times higher for atrazine than for chlorpyrifos (8.0 vs. 4.1, respectively).

Residential Pesticide Use

Residential pest treatments were common, with treatment of non-termite insects (52%) being the most prevalent, followed by fleas on pets (39%), weeds (37%), termites (15%), and fleas in the home (3%) (Table 2). Chlorpyrifos is an insecticide that was commonly used at enrollment. All three types of insect treatments had a ≥1% probability of containing chlorpyrifos (Supplemental Table S2), and therefore all contributed to the estimated exposure estimate among spouses reporting the given treatment. The $k_{termites}$ value was 1.5, $k_{insects}$ was 1.3, $k_{fleas\ home}$ was 1.3, and $k_{fleas\ pets}$ was 1.3. As with all insecticides, the k_{weeds} for chlorpyrifos was 0 (Supplemental Table S2). Of the 19,064 spouses with complete information on chlorpyrifos, 11,999 (63%) were estimated to be exposed via the residential pesticide use pathway (*i.e.,* E_{res}>0). Among those exposed, the median (IQR) exposure intensity estimate was 40 (27–75), yielding a ratio of 75th to 25th percentiles of 2.8.

Atrazine is an herbicide, and thus only weed treatments had the potential to contribute to atrazine's residential pesticide use exposure intensity estimate. Because atrazine had low probability of use in any consumer products, only spouses reporting treatments by "professionals" or "both household members and professionals" or an "other" or "unknown" person had a ≥1% probability and contributed to the residential pesticide use exposure intensity (Supplemental Table S2). Of the 6,999 spouses reporting a weed treatment, only 881 were estimated to be exposed to atrazine via the residential pesticide use pathway (5% of the population with complete atrazine data) (Table 2). Among those exposed, the median (IQR) was 33 (19–45) intensity-weighted years, yielding a ratio of 75th to 25th percentiles of 2.4. The median and IQR intensity-weighted residential use estimate for exposed spouses were higher and broader for chlorpyrifos vs. atrazine (median 40 vs. 33, respectively; IQR 27–75 vs. 19–45, respectively) (Table 2).

Integration of the Three Pathways

Total non-occupational exposure intensity ($E_{non\text{-}occ,\ ai}$) was calculated by summing each pathway, assuming the resulting exposure from the three pathways is additive. While the proportion of spouses with non-zero estimates for total non-occupational exposure intensity were nearly identical (78% and 77% of the population for chlorpyrifos and atrazine, respectively), the prevalence and magnitude of exposure intensity for the specific pathways differed for these two active ingredients. Among those with $E_{non\text{-}occ}$ >0, the median (IQR) was 39 (19–73) for chlorpyrifos and 16 (5.4–38) for atrazine.

The Spearman correlations between pathways among spouses with total, non-occupational exposure >0 are shown in Table 3. For chlorpyrifos, the-take home and drift exposure intensity estimates were almost perfectly positively correlated with each other ($r_{Spearman}$=0.99), but each was not correlated with the residential use pathway ($r_{Spearman}$=0.02 for take-home and $r_{Spearman}$ =0.01 for drift) (Table 3). Neither the take-home nor drift pathways were strongly correlated with the total, non-occupational exposure for chlorpyrifos ($r_{Spearman}$=0.31 for each), whereas the residential pesticide use pathway was highly correlated with the total non-occupational exposure intensity ($r_{Spearman}$=0.90). For atrazine, the take-home and drift exposure intensity estimates were also highly correlated ($r_{Spearman}$=0.98) and were highly correlated with the total, non-occupational exposure intensity ($r_{Spearman}$=0.96 for each) (Table 3). For atrazine, the residential pesticide use pathway was not correlated with either the take-home or drift pathways ($r_{Spearman}$=0.02 for each), and was only weakly correlated with total non-occupational exposure intensity ($r_{Spearman}$=0.24).

DISCUSSION

We developed a deterministic algorithm based on subject-level information and quantitative synthesis of published exposure data to assign quantitative, cumulative married lifetime estimates of pesticide exposure intensity from three non-occupational exposure pathways.

This algorithm fills an important gap that provides for better identification of differences in cumulative pesticide exposure intensity among the AHS spouses, a population that presumably experiences higher non-occupational exposures than the general population because of their proximity to agricultural pesticide uses. Application of this algorithm to the AHS spouses demonstrated a wide distribution of cumulative exposure intensity estimates for two active ingredients, supporting use of the algorithm in future etiologic analyses, potentially advancing our understanding of non-occupational pesticide exposure on chronic health outcomes. Our systematic approach and the transparency of our assumptions will allow the algorithm to be revised as new information becomes available and will allow for sensitivity analyses that examine the impact of our assumptions on exposure-response relationships.

Development of the algorithm to refine exposure intensity estimates for AHS spouses beyond previously used simpler metrics, such as ever/never use of a specific pesticide (Louis et al. 2017; Lerro et al. 2015; Engel et al. 2005) or whether the applicator applied a specific pesticide (Engel et al. 2005; Engel et al. 2017), required several assumptions necessitated by the study design, the types of information collected in the AHS, and the availability of published data, which we describe below. We strove to align the information from the AHS questionnaire with the evidence in the literature. Although the development of this algorithm often involved assumptions or imperfect proxies, we expect that the algorithm's use will reduce exposure misclassification over previously used metrics and will improve our ability to evaluate risk in this population. Although exposure misclassification will remain a concern, it is expected to be non-differential, because the information from the spouses and applicators was largely obtained prior to diagnosis of diseases.

Pathway-specific, questionnaire-based exposure surrogates

The take-home pathway described here takes into account the over two-times increase in house dust pesticide concentrations reported in the literature in homes of farmers applying pesticides and the AHS applicators' pesticide use patterns, with a modifier that represented the AHS spouses' time spent in or around the home, because increased time at home increases the likelihood or amount of contact with pesticides that enter the home from the applicator's activities. This time modifier was based on the spouse's longest-held off-farm job due to the lack of a full occupational history. It was also based on the 2003 American Time Use Survey of women in non-metropolitan areas, which we assumed was representative of the predominantly rural population and earlier years.

The agricultural drift pathway takes into account the observed exponential decrease in house dust pesticide concentrations with increasing distance from treated fields and the applicators' pesticide use patterns. We assumed that self-reported distance to fields was relevant to all active ingredients used by the applicator, as pesticide-specific distance was not queried. In addition, we assumed that the nearest treated field was the applicator's field, because the distance question did not distinguish between the applicators' fields and their neighbors' fields. A more accurate measure of distance to fields could in future efforts use geocoded residential addresses and state crop maps that could better account for pesticide drift from nearby farms. Application quantity, application methods, pesticide formulations, or acreage of crops treated may be more accurate predictors of pesticide concentrations in house dust (Gunier et al. 2011); however, adding these refinements would require re-contacting applicators and obtaining additional information. Meteorological conditions (e.g., wind direction, wind speed, temperature) are important factors predicting agricultural drift, but accurately incorporating these factors would require historical data on meteorological conditions in conjunction with knowledge about where and when pesticides were applied in relation to the home, which is not available for this population.

The residential use pathway accounted for the observed increased pesticide concentration in house dust from multiple pest treatment types. Although information on active ingredients in these treatments was not collected in the AHS questionnaires, an active ingredient-specific estimate was made possible by using the NCI pesticide exposure probability matrix to link treatment types to probable active ingredients. The nation-wide population-based weights from the pesticide matrix applied to these agricultural residents may over- or underestimate exposure to specific active ingredients at the individual level. Differences in residential pesticide exposure intensities based on whether the spouse or another household member performed the treatment was only partially taken into account with applicator-specific (e.g., household member vs. commercial applicator) probabilities of use in the pesticide exposure matrix of a specific active ingredient. We did not have consistent, detailed information on the frequency and duration of residential pest treatments and therefore assumed the reported treatment was representative of usual usage patterns over the years the spouse and applicator lived together. Our approach averages probabilities and treatment practices over time and therefore may not capture changes in formulations due to economic changes or regulatory actions. In addition, this approach may not capture a pesticide if its usage does not fit into one of the survey categories. Finally, the weights derived for this pathway focused on patterns observed in rural populations, which may not be applicable to urban settings. The *Years Together* component of the residential-use pathway will require customization for each active-ingredient based on when it was approved for in-home use. For instance, many organochlorine pesticides were banned in the United States in the 1970s and 1980s and therefore, the *Years Together* variable should be truncated to the year the use of a specific organochlorine active ingredient of interest was restricted. The impacts of the assumptions made for the residential use pathway and its contributions to cancer risk can be examined in sensitivity analyses.

Literature-based pathway-specific weights

The framework's pathway weights were data-driven, with confidence intervals, and were based on a novel application of meta-regression models to synthesize published environmental data to capture broad contrasts in relative contributions (Deziel et al. 2017). An additional advantage of this approach is that the distribution of pathway weights could be used to estimate uncertainties in the exposure assessment. The weights reflect summary effects across a range of different pesticide compounds, thereby increasing the generalizability of the equations. However, these data-driven weights did not identify finer nuances in exposure intensity because, at this time, data were too sparse to confirm quantitative differences in pathway weights for various subgroups, such as pesticide type, active ingredient, formulation type, crop type, application method, geographic location, or time period. Some subgroup-specific differences were previously identified, but were based on small numbers (Deziel et al. 2017). For example, the relative increase in house dust pesticide concentrations in homes of farmers with more frequent vs. less frequent pesticide contact was higher for atrazine compared to chlorpyrifos, though the difference was not statistically significant. Also, the decrease in house dust pesticide concentrations with increasing distance between homes and treated fields was greater for herbicides compared to insecticides. The weights might be able to be adjusted for specific chemicals based on their unique physicochemical properties, such as their transport potential or persistence. The transparency of this approach allows for weights to be recalculated and sensitivity analyses repeated if new data become available.

The pathway weights were based on an important assumption that pesticide concentrations in house dust serve as a reasonable proxy for adult exposure. Although dust pesticide concentrations are a potentially useful exposure indicator in children (Bradman et al. 1997), their relevance to adult exposure is less established (Butte and Heinzow 2002). We used house dust pesticide concentrations as a surrogate for chronic exposure because pesticides in indoor dust resist degradation due to limited sunlight, microbial activity, and moisture (Simcox et al. 1995; Lewis et al. 1994). Biological monitoring data from spouses/women in agricultural areas, a more direct measure of exposure, was not used here to predict exposure contrast, because pesticide biomarkers tend to have low percent detection and limited variability within study populations, and generally reflect recent exposures (Arbuckle and Ritter 2005; Arbuckle et al. 2006; Deziel et al. 2015b; Mandel et al. 2005). More research is needed on the relevance of house dust for predicting cumulative, adult exposure to pesticides in agricultural populations. Another challenge with dust pesticide measurements is that they integrate the three exposure pathways. We strove to disentangle the relative contribution or weight of each of the non-occupational pathway wherever possible by basing the data-driven weights on published exposure estimates that adjusted for the other exposure pathways (Deziel et al. 2017).

Application of algorithm and correlations among pathways

Application of our algorithm to two pesticides illustrated some important pathway-specific distinctions in estimated exposure intensity by active ingredients. For atrazine, the take-home and drift pathways were dominant, whereas the residential pesticide use pathway was diminutive. In contrast, for chlorpyrifos, the residential pesticide use pathway was a greater contributor to cumulative, non-occupational exposure than the pathways related to the applicator's pesticide use.

The take-home and agricultural drift pathways were highly correlated with each other for both active ingredients ($\geq$0.98), due to the common equation components related to the applicators' duration and frequency of pesticide use. Though users of the algorithm may retain only one of these pathways in the algorithm, in this analysis we chose fidelity to the exposure literature, which suggests an independent contribution of each pathway, versus parsimony and simplicity. The impacts of this choice can be examined in sensitivity analyses. New evidence may provide improved information for disentangling these two pathways.

Omitted pathways and time periods

The algorithm captures the three exposure pathways with the strongest empirical evidence. However, at this time the algorithm does not capture all potential non-occupational exposure sources or time periods for the spouses and is expected to non-differentially underestimate non-occupational cumulative exposure intensity. Possibly the most important underestimation of exposure occurs from our inability to characterize exposure for the time window prior to the spouse's marriage to the applicator, because active ingredient-specific information for this earlier time period was not included in the AHS questionnaires. This may be important for the 58% of the AHS spouses who reported living most of their life on a farm prior to age 18 (Hofmann et al. 2015), particularly given the mounting evidence that early-life exposures to environmental chemicals can lead to increased risk of chronic diseases in adult life (Barouki et al. 2012). An accounting of these earlier-life exposures would require re-contacting the spouses, and even then, they may not be able to reliably report use of specific active ingredients on their childhood farms.

Underestimations of non-occupational exposure may also occur from omitting the dietary exposure pathway; however, our previous literature review found only limited evidence that dietary factors were linked to increased pesticide exposure in farming populations (Deziel et al. 2015b). We also omitted the bystander pathway (incidental exposure from being present but engaged in an unrelated activity at the time of pesticide application) because of limited published data quantifying its contribution (Deziel et al. 2015b) and lack of information on the timing of pesticide applications during AHS spouses' field-based tasks. For instance, we previously identified only three publications with relevant data that demonstrated a short-term increase in urinary pesticide biomarker concentrations among a limited number of female spouses who were "outside" or "nearby" when their husbands conducted liquid spray applications (Alexander et al. 2006; Alexander et al. 2007; Arbuckle and Ritter 2005). Additional studies that more precisely define bystander exposure and examine a greater number of spouses over a longer time period and different application scenarios would be informative. Further, we were not able to identify a suitable surrogate for bystander potential from the AHS questionnaire data. We considered using days spent in the field or data on spouse engagement in farm activities as proxies for the probability of being a bystander; however, we concluded that many of the queried activities would not likely coincide with timing of pesticide applications.

Additional underestimations of exposure may occur within the three pathways evaluated here because the estimates of drift and take-home exposure intensity do not include pesticide usage of the other residents in the home (including the spouses) or neighboring farmers/ farmworkers. The spouses' usage could be included in sub-analyses or sensitivity analyses. Incorporation of other household member applications for the take-home pathway would require re-contacting participants or their family members. Neighbors' pesticide usage may be incorporated eventually into the drift pathway using crop maps to predict which active ingredients were applied to neighboring farms. Underestimation of exposure may also occur because the algorithm omits non-occupational pesticide exposure at the spouse's off-farm jobs. No information was collected on active ingredient-specific pesticide applications in or near the spouse's work place. Finally, the model did not modify exposure intensity for hygiene-related factors, such as removing work clothing and shoes prior to entering the home or in-home cleaning practices; however, we previously identified only limited support for the impact of these behaviors on house dust pesticide levels (Deziel et al. 2015b).

Use of algorithm and future efforts

This algorithm was designed for the AHS spouses; however, it may have relevance to a broader population, including children living on farms or residents of agricultural areas. Approximately 2% of the U.S. population lives on farms, while 15% live in rural areas, potentially in proximity to crops or orchards where pesticides are applied (U.S.D.A. 2009, 2015). In addition, approximately 80–90% of households in both urban and rural areas report using pesticides for home and yard pest treatments (Adgate et al. 2000; Colt et al. 2004; Deziel et al. 2015a; Wu et al. 2011). The framework may be extended with some modification for the population of interest and the study-specific information available. The algorithm is intended to be used separately for individual active ingredients; use of the algorithm to assess health impacts from combining exposure intensities from the algorithm across multiple pesticides would require consideration of the relative toxicokinetic and toxicological properties of the different chemicals.

Ideally, the algorithm's intensity scores require validation, but this is difficult because of a lack of a gold standard over the time frame of interest; as such any current validation studies would require extrapolation or generalization to historical exposures. However, there may be informative value to relate estimates of exposure intensity with shorter-term measurements of exposures to provide an indication of the degree of exposure misclassification associated with surrogate indicators (Blair et al. 2011). In future efforts, we will evaluate the validity of the algorithm by determining whether the intensity estimates are associated with pesticide dust concentrations. These evaluations will be similar to those conducted to examine the validity of the applicator's occupational algorithm (Coble et al. 2005; Thomas et al. 2010; Hines et al. 2008). In addition, we plan to conduct indirect validation of these metrics by evaluating how exposure-response relationships change when using the newly developed algorithm as compared to simpler metrics. We will also examine consistency between exposure-response relationships in the AHS spouses and associations that were previously observed in the applicators based on occupational exposure. Finally, we will investigate the impact on the exposure-response relationships when certain pathways are included or excluded. For instance, because it is uncertain whether the spouse's self-reported employment status is a good surrogate for the potential for take-home exposure, we can examine the impact on pesticide exposure intensity estimates that include or exclude the take-home pathway.

CONCLUSIONS

In summary, we developed a deterministic algorithm to provide a metric of cumulative, active ingredient-specific pesticide exposure intensity for AHS spouses that represents additional exposure refinement over using questionnaire variables singly or accounting only for their personal use of pesticides. Our algorithm captured substantial contrast in exposure intensities within the study population and demonstrated important pathway-specific differences for two active ingredients. The transparency of our assumptions and systematic analysis of the published data will allow for future sensitivity analyses that examine the influence of our assumptions on the rank ordering of participants. The approach allows for the algorithm to be readily revised as new information becomes available, and for possible adaptations to other study populations. The algorithm represents an important step forward in identifying pesticide exposure contrast in the AHS spouses. Subsequent etiologic analyses based on our exposure assessment approach have the potential to advance greatly our understanding of the potential health risks pesticides pose to women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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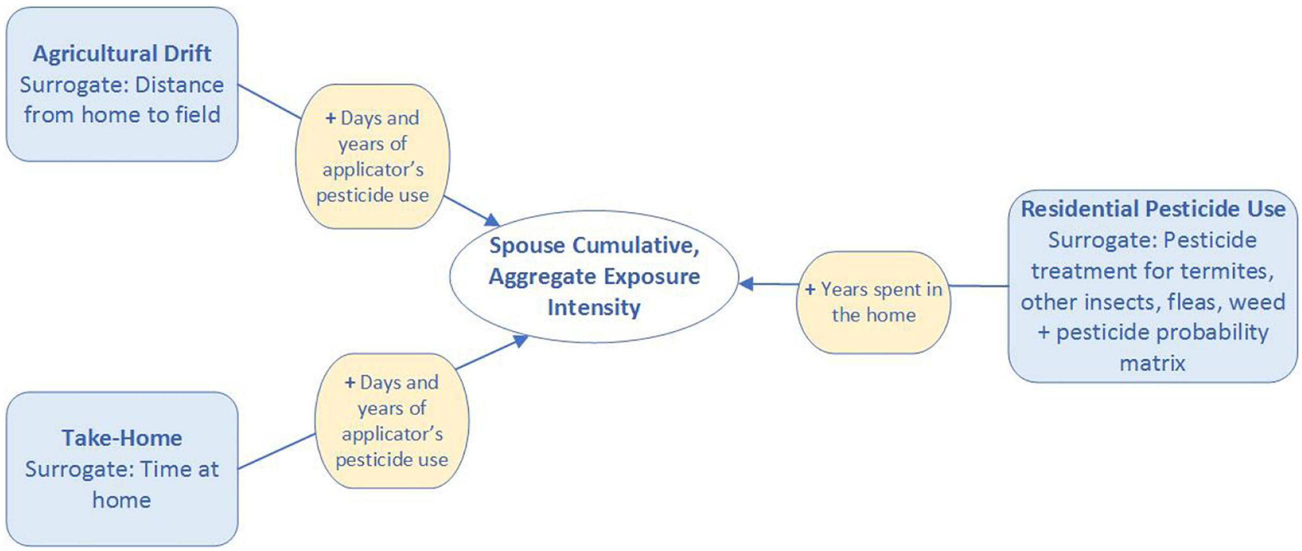

Figure 1.

Conceptual framework for non-occupational pesticide exposure algorithm.

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Table 1.

Agricultural drift exposure: Data-derived weighting factors based on the distance between residence and treated fields.

Questionnaire Response Categories[a]	Distance (ft)[b]	Predicted GM Concentration (μg/g)[c]	k_{drift} (95% CI)[d,e]
<100 yd	150	0.13	3.0 (1.7, 5.4)
100–199 yards	450	0.08	1.9 (1.4, 2.6)
200–299 yards	750	0.07	1.5 (1.2, 1.9)
>300 yards or more	1350	0.05	1.2 (1.1, 1.3)
>1/4 mile (Ref)[f]	1980	0.044	1.0
No pesticides applied on farm			1.0

[a] Questionnaire item: "How far is your home from the nearest field or orchard where pesticides are applied?" Response category units reflect those on the questionnaire (English units).

[b] Distance was assigned the mid-point of the range of the self-reported category or 1.5 times the lower bound. Note that 100 ft = 30.5 m.

[c] Calculated using the formula *Predicted GM*=distance$^{-0.43}$ e$^{0.15}$, from Equation 13 in Deziel et al. 2017.

[d] Relative increase in GM pesticide concentrations relative to the reference group ($GM_{Distance}/GM_{Ref}$).

[e] Confidence intervals calculated using formula Lower CL = exp(−0.21* ln(distance/distance$_{Ref}$)) and Upper CL=exp(−0.65* ln(distance/distance$_{Ref}$)) based on confidence limits on the LogDistance regression parameter from Table 4 in Deziel et al. 2017.

[f] Reference category of 1980 ft was based on 1.5 times a quarter mile, the farthest distance category queried in a follow-up questionnaire (Phase 2) of the AHS.

Table 2.

Distributions of subject-specific pathway components and cumulative estimates of non-occupational exposure intensity for atrazine and chlorpyrifos for AHS spouses with complete information.

Pathway Components	Chlorpyrifos (Insecticide) (N=19,064)[a] N (%)	Atrazine (Herbicide) (N=19,077)[a] N (%)
Applicator-husband applied active ingredient		
No	10,762 (56%)	4,596 (24%)
Yes	8,302 (44%)	14,481 (76%)
Take-home		
Hours per Day Spouse at Home		
Full-time off-farm job (15.6 hr)	13,920 (73%)	13,923 (73%)
Part-time off-farm job (17.8 hr)	3,345 (18%)	3,353 (18%)
No off-farm job (21.0 hr)	1,799 (9%)	1,801 (9%)
Drift		
Distance (ft) between house and fields (d) [corresponding k_{drift} value][b,c]		
150 [3]	8,879 (47%)	8,907 (47%)
450 [1.9]	3,832 (20%)	3,829 (20%)
750 [1.5]	1,308 (7%)	1,302 (7%)
1350 [1.2]	4,216 (22%)	4,215 (22%)
1950 [1.0]	829 (4%)	824 (4%)
Residential Treatments		
$Treated_{termites} = Yes$	2,946 (15%)	2,944 (15%)
$Treated_{insects} = Yes$	9,814 (51%)	9,843 (52%)
$Treated_{fleas\ home} = Yes$	629 (3%)	632 (3%)
$Treated_{fleas\ pet} = Yes$	7,484 (39%)	7,495 (39%)
$Treated_{weeds} = Yes$	6,978 (37%)	6,999 (37%)
Exposed via residential use pathway (>0 probability of active ingredient)	11,999 (63%)	881 (5%)
	Median (IQR), Exposed spouses	**Median (IQR), Exposed spouses**
Duration Metrics, exposed subjects[b]		
Years Applicator Applied While $Together_{ai}$ (yr)	3.5 (3.5–8.0)	8.0 (3.5–25.5)
Days Applicator $Applied_{ai}$(d/yr)	7.0 (2.5–7.0)	7.0 (2.5–14.5)
Pathway estimates, exposed subjects		
$E_{take\text{-}home,ai}$[d] **(intensity-weighted yr)**	2.5 (0.9–6.6)	5.8 (2.1–15)
$E_{drift,\ ai}$[e]	4.1 (1.7–11)	8.0 (2.6–22)
$E_{res,ai}$[f,g]	40 (27–75)	33 (19–45)
$E_{non\text{-}occ,ai}$[h]	39 (19–73)	16 (5.4–38)

[a] Number of spouses with complete information for an active ingredient. See Methods section for inclusion criteria/how "complete information" defined.

[b] All reported statistics based on those exposed to the active ingredient.

[c] Kdrift values obtained from Table 1.

[d] Equation 2

[e] Equation 3

[f] Treatment and active ingredient specific weights provided in Supplemental Tables S1 and S2.

[g] Equation 4

[h] Equation 1

Note: Algorithm inputs with constant values: *Median Application Days* = 14.5 d/yr, $k_{take\text{-}home}$=2.3; $k_{termintes,chlorpyrifos}$=1.5, $k_{insects,chlorpyrifos}$, $k_{fleas\ home,chlorpyrifos}$, $k_{fleas\ pets,chlorpyrifos}$ = 1.3, $k_{weeds,chlorpyrifos}$=0; $k_{termintes,atrazine}$=1.5, $k_{insects,atrazine}$, $k_{fleas\ home,atrazine}$, $k_{fleas\ pets,atrazine}$ = 1.3, $k_{weeds,atrazine}$=0

Table 3.

Correlations among pathway-specific exposure-intensity estimates for chlorpyrifos and atrazine.

	Spearman Correlation Coefficients			
	Take-home	**Agricultural Drift**	**Residential Use**	**Total Non-Occupational**
Chlorpyrifos, spouses with $E_{non\text{-}occ}$ >0 (n=19,064)				
Take-home	1.0	0.99 *	0.02	0.31 *
Agricultural Drift		1	0.01	0.31 *
Residential Use			1	0.90 *
Atrazine, spouses with $E_{non\text{-}occ}$ >0 (n=19,077)				
Take-home	1	0.98 *	0.02	0.96 *
Agricultural Drift		1	0.02	0.96 *
Residential Use			1	0.24 *

* p<0.001